REMARKS

With this amendment, claims 1-19 are pending. Claims 1 and 3 are amended. Support for the amendments is found, e.g., at page 26-27 and elsewhere throughout the specification. No new matter is introduced by the amendments, which are clarifying in nature. Applicants traverse all rejections as they may be applied to the amended claims, for the reasons noted herein.

RESTRICTION

Applicants appreciate the Examiner's helpful indication that groups IV and V were rejoined as urged by Applicants. In the event that one or more divisional applications are filed, the new grouping will be used as the basis for such divisional applications. Withdrawn claims have been canceled, per the restriction requirement made final.

IDS

Applicants appreciate the Examiner's indication that the IDS filed 1/03/2006 has been considered.

AS AMENDED, THE CLAIMS ARE NOVEL OVER BANDMAN

Claims 1-2 were rejected over Bandman et al. (US 6,274,138). To the extent that the rejection may be applied to the amended claims, Applicants traverse.

The rejection argues that Bandman et al. teach the same polypeptide as SEQ ID NO:4 of the subject application, and that, therefore, claims 1-2 are anticipated. Applicants do not agree. SEQ ID NO:4 is not claimed, nor do the original or amended claims read on SEQ ID NO:4. The claims require that the relevant polypeptide have DNA nuclease activation activity or cell killing activity. **SEQ ID NO:4 simply does not have this activity.**

Applicants appreciate the Examiner's indication that the Office can not evaluate whether prior art compositions have a claimed activity and that the Examiner cannot investigate whether SEQ ID NO: 4 has the claimed properties of the claimed composition. However, this is not an issue in the present case. Applicants have already

provided evidence that SEQ ID NO:4 *does not have the claimed activity*. As taught in detail in the application, the full length mature MDH enzyme, corresponding to SEQ ID NO:4 *does not have DNA fragmentation activity*. See, e.g., page 35, and, e.g., page 116-117. As demonstrated, the full length MDH polypeptide, which is 36 kDa in size, *has no fragmentation activity*. In contrast, as Applicants quite *surprisingly* discovered, a degradation breakdown product of the full-length MDH polypeptide, e.g., an N-terminal 9kDa fragment, starting at residue 215 of the full-length polypeptide, induced DNA fragmentation.

The Action's arguments regarding the doctrine of anticipation by inherency are also equally misplaced. For a prior art teaching to anticipate by inherency, the relevant limitations of the claim must be "necessarily present.[1]" This basic test flatly cannot be met by Bandman. In fact, nothing in Bandman relates, in any way, to the claimed invention. Bandman simply does not teach an MDH polypeptide that induces DNA fragmentation. At most, the reference relates generally to the MDH enzyme, which is not claimed in the current case. The issue is **not** whether nuclease activation activity was "recognized" by Bandman—the issue is simply that no specific MHD fragment that comprises nuclease activity is described, at all, by Bandman. The rejection must be withdrawn.

AS AMENDED THE CLAIMS ARE NOVEL OVER TANG

Claims 1-5, 8 and 17 were further rejected for alleged anticipation by Tang et al. (WO 01/66689). Applicants traverse.

---

[1] Continental Can Co. USA v. Monsanto Co., 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991): To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill. *In re Oelrich*, 212 USPQ 323, 326 (C.C.P.A. 1981) (quoting *Hansgirg v. Kemmer*, 40 USPQ 665, 667 (C.C.P.A. 1939)) provides: Inherency, however may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

As a preliminary matter, only page 1 of Tang et al. was provided to the Applicants. In reviewing Tang et al. on line from WIPO (WO 01/66689 A2), in an attempt to determine the basis for the rejection, it appears that no sequences are provided in the published reference, making the relevance of Tang et al. rather unclear. However, certain of the priority documents for Tang et al., also provided on line by WIPO, include over 600 hundred pages worth of sequence listings. Applicants take the Examiner's argument to be that one of these many thousands of sequences (see also Tang et al. claim 1) includes an MDH sequence that is the same as SEQ ID NO:4 of the subject application.

Even taking the Action's statements regarding the presence of an MDH sequence in Tang, *arguendo*, as correct, the reference still completely fails to disclose a polypeptide with the claimed activity. The Action essentially argues that Tang teaches a mature form of MDH coupled to various targeting moieties. While Applicants do *not* agree that Tang specifically teaches any such fusion[2], this interpretation of Tang still completely fails to state a case for anticipation. The full length mature MDH *does not have nuclease activation or cell killing activity.* No fragment of MDH that does possess these properties is taught by Tang or alleged in the Action. The reference, therefore, completely fails to meet the limitations of the claims. The rejection must be withdrawn.

AS AMENDED THE CLAIIMS ARE NOT OBVIOUS

Claims 9-16 were rejected over Tang et al. in view of Wang (Cancer Research 1991, 51:3353). Applicants traverse.

There are three basic requirements that must be met in establishing a *prima facie* case of obviousness. First, the limitations of the claims must be taught by the references. Second, the motivation to combine the references must be found in the prior art. Third, there must be a reasonable expectation in the prior art that the combination will result in the invention. MPEP § 2143. None of these requirements can be met in the present case.

---

[2]as noted, Tang, allegedly, provides a list of over 6,000 sequences coupled with generic possible use statements, none of which are specifically linked with any specific sequences (allegedly) provided, for any specific purpose whatsoever.

First, nothing in the combination of references teaches the basic limitations of the claims. Even taking the Action's interpretation of the Tang sequences, *arguendo*, as being correct, Tang et al., at most, teach the mature MDH polypeptide. Wang teaches nothing regarding MDH or fragments thereof. Neither Tang nor Wang teach anything regarding an MDH fragment with nuclease activation/cell killing activity. As discussed above, the mature MDH polypeptide is simply devoid of the claimed activity. The combination of references, therefore, flatly fails to teach the claimed invention.

There is also no specific basis for the combination of references alleged that can be found in the prior art. The Action alleges that Tang et al. teach that the MDH polypeptide may be useful in cancer treatment, citing page 52, arguing that treatment of specific cancers is taught in Wang. Applicants disagree.

Tang does not teach anything at all regarding anti cancer activity of any MDH polypeptide or fragment. At best, Tang (allegedly) lists several thousand nucleic acid and peptide sequences, one or more of which relates to MDH (as noted above, the sequences do not actually appear in the published version of the Tang application, so even this relationship is unclear). Tang et al. then allege that "some" of the sequences "may" have any of a variety of activities listed on pages 39-60 of Tang. That is, the reference apparently lists more than 6,000 sequences (see Tang et al., claim 1), and then alleges that some of them may (or may not) have one or more activity listed on a 21 page list of activities. This is not a meaningful teaching to one of skill regarding any *specific* polypeptide activity for any specific polypeptide. It could just as easily be stated that somewhere in Genebank there may or may not be a gene that is involved with one or more medical disorder found in Harrison's Guide to Internal Medicine. This would not invalidate a later invention that relies upon a discovery of a specific association between a gene and a disease, because, while the statement that Genebank might include some disease related genes is true, it is also meaningless in any practical sense.

In any case, even if one of skill were to decide that there is an MDH gene taught by Tang and that this gene is somehow associated with cancer treatment, they would probably be wrong. As noted, mature MDH does not have DNA fragmentation/

cell killing activity, so it is utterly unclear what effect targeting mature MDH to cancer cells would have. Indeed, Bandman (6,274,138) argues that MDH is useful in treating vesicle trafficking disorders (column 19), rather than cancer. In light of Bandman, one of skill would not have interpreted the purely generic statements of Tang et al. at page 53 as relating to the MDH polypeptides at all, but, rather to one or more of the other (6000+?) polypeptides allegedly recited by Tang.

Finally, there is no evidence of record that a combination of Tang and Wang would be useful as a treatment for cancer. At most, the Action's allegation is that the mature MDH (allegedly provided by Tang) could be targeted to cancer cells (per Wang) to kill them. However, given that mature MDH is not particularly cytotoxic—it mediates oxidation of NADH, rather than DNA fragmentation—it is not clear what mechanism of action is even being proposed by the combination. Put another way, why would increasing NADH oxidation result in cytotoxicity of targeted cancer cells?

Accordingly, none of the basic criteria for establishing obviousness can possibly be met in the present case, and the rejection should be withdrawn.

Claims 6-7 were further rejected over Tang in combination with Sherman, while claims 17-20 were further rejected over Tang in combination with Ungar. Applicants traverse.

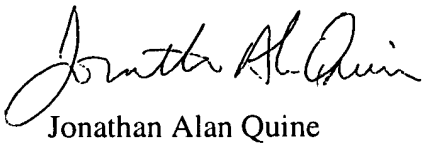
These rejections present essentially similar issues to those already addressed in detail above. No combination of the cited references can meet the most basic requisite of establishing a prima facie case of obviousness, i.e., no combination of references provides an MDH fragment that displays nuclease activation activity. In addition, no case for combining Tang with Sherman or Ungar can be made 1) because Tang teaches nothing regarding activity of MDH, making it impossible to establish any motivation combine this reference with any other in the manner suggested; and 2) because mature MDH does not have nuclease activation activity, as apparently supposed in the rejections, there is no expectation that any such combination would successfully produce anything useful, let alone the claimed invention. These rejections must, therefore, also be withdrawn.

CONCLUSIONS

Applicants request a notice of allowance at an early date. In the event that an additional office action is contemplated, **Applicants respectfully request an Examiner Interview PRIOR to any additional action on the merits.**

QUINE INTELLECTUAL PROPERTY LAW GROUP
P.O. BOX 458, Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877
PTO Customer No.: **22798**
Deposit Account No.: **50-0893**

Respectfully submitted,



Jonathan Alan Quine
Reg. No: 41,261

Attachments:

1) A petition to extend the period of response for **3** months;
2) A transmittal sheet;
3) A Fee Transmittal sheet and,
4) A receipt indication postcard.